General

Guideline Title

Abnormal liver chemistry—evaluation and interpretation.

Bibliographic Source(s)

Medical Services Commission. Abnormal liver chemistry - evaluation and interpretation. Victoria (BC): British Columbia Medical Services Commission; 2011 Aug 1. 5 p. [14 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Diagnosis/Investigation

Abnormal liver tests may indicate an abnormality of the liver and provide clues as to the nature of the problem. However, in an asymptomatic patient, mild abnormalities may not be clinically significant. A systematic approach to evaluating the patient and ordering further tests will help to identify underlying disease. Further testing and referrals may not be necessary in many circumstances.

The term 'liver function test' should not be used when referring to serum enzyme levels because they correlate poorly with metabolic activities of the liver.

There are two broad categories of liver enzyme abnormalities: hepatocellular and cholestatic. Usually the most marked abnormality points to the underlying category of disorder.

1. Hepatocellular injury (e.g., hepatitis)
   The membranes of liver cells can become permeable when damaged, allowing for escape of intracellular enzymes into the bloodstream. The major intracellular enzymes are alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

2. Cholestasis (e.g., biliary obstruction or hepatic infiltration)
   Obstructed/damaged intra- or extra-hepatic bile ducts cause the induction of synthesis of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). In acute biliary obstruction, elevation of these enzyme levels often lags obstruction by approximately 24 hours. An isolated minor elevation of GGT is a relatively common finding and does not necessarily indicate significant liver disease.

Note: Serum bilirubin is not a useful test for distinguishing between cholestasis and hepatocellular injury because it may be elevated in both

situations.

History and Physical Exam

Obtain a history to determine risk factors for liver disease.

Table: Risk Factors for Liver Disease

High Risk Behaviour • IV drug use (past and present) • Multiple sexual partners • High-risk sexual activity • Tattoos • Nonsterile body piercing • Alcohol abuse	Systemic Illness • Diabetes • Obesity • Hyperlipidemia • Iron overload • Autoimmune diseases • Metastatic cancer • Inflammatory bowel disease
Commonly Implicated Medications • Acetaminophen, NSAIDs • Antibiotics (e.g., clavulanic acid-amoxicillin, nitrofurantoin, sulfonamides) • HMG-CoA reductase inhibitors (statins) • Anticonvulsant drugs (e.g., phenytoin, carbamazepine, valproic acid) • Isotretinoin (Accutane®) • Immunomodulators (e.g., methotrexate, azathioprine) • Antituberculous drugs (e.g., isoniazid) • Some herbal medications	Other • Travel to or residence in less developed regions or countries • Needlestick injury or other occupational exposure (e.g., razors) • Receipt of unscreened blood products, especially prior to 1990* • Hemodialysis • Contaminated food or water (hepatitis A)

HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs

*Screening of donated blood products for hepatitis C (anti-HCV) began in 1990 in Canada

Perform a physical examination to look for evidence of liver disease.

Table: Common Clues to Diagnose Liver Disease

Symptoms/Signs	Level or Stage of Liver Disease
Jaundice	Acute hepatitis, biliary obstruction, or advanced chronic liver disease
Abdominal pain, fever	Acute cholangitis, cholecystitis or liver abscess
Chronic stigmata: spider angiomata, palmar erythema, gynecomastia, testicular atrophy, asterixis	Cirrhosis
Complications: encephalopathy, ascites, acute gastrointestinal bleeding, coagulopathy, muscle wasting	Advanced liver disease (decompensated)
Chronic generalized pruritus	Cholestasis (e.g., primary biliary cirrhosis)

Initial Investigations

If liver disease is suspected, but the cause is not apparent from the initial history and physical examination, direct further investigations towards

determining whether the condition is predominantly hepatocellular or cholestatic. Order ALT and ALP at this time.

In patients with clinically overt hepatobiliary disease, it may be expeditious to include an AST and GGT with the initial blood work. Do not order GGT and lactate dehydrogenase (LDH) in isolation for initial investigation of possible liver disease. Isolated elevation of GGT is nonspecific but may indicate overuse of alcohol and become a useful tool for counselling a patient where alcohol abuse or dependence is a concern.

Cholestasis

If ALP elevation is the predominant abnormality, obtain GGT to confirm hepatobiliary origin. If cholestasis is confirmed, then perform abdominal ultrasound to assess the biliary tree. If ALP and GGT are elevated in the setting of a non-dilated biliary tree, then intra-hepatic cholestasis or hepatic infiltration is suggested. If the biliary tree is dilated, then determine the cause of obstruction.

If GGT is not elevated, then an elevated ALP may be of bone or placental origin.

Hepatocellular Injury

Predominant ALT elevation points to hepatocellular damage. A detailed patient history will help delineate risk factors and potential causes.

Presentation with an ALT exceeding 1000 U/L usually represents one of the following conditions: acute viral hepatitis, acute choledocholithiasis, acute vascular injury of the liver (ischemia or congestion) or ingestion of hepatotoxin (e.g., acetaminophen, poisonous mushrooms).

Test for viral causes in accordance with the Viral Hepatitis Testing guideline available at www.BCGuidelines.ca. Consider other causes of liver disease (see the table below). If iron overload is being considered, refer to Iron Overload - Investigation and Management available at www.BCguidelines.ca.

Table: Enzyme Elevations in Liver Disease

	Abbreviation *Full Name*	When Is It Likely to Be Abnormal	Specificity for Liver Disease	Other Causes
Hepatocellular injury (Hepatitis – all types)	ALT *Alanine aminotransferase*	Hepatitis (particularly viral, autoimmune, drug induced, non-alcoholic fatty liver disease [NAFLD], iron overload)	Sensitive and specific	Acute obstructive jaundice (within first 24h)
	AST *Aspartate aminotransferase*	Hepatitis (particularly alcoholic), hepatic fibrosis/cirrhosis	Less sensitive and specific than ALT	Cardiac or skeletal muscle injury or hemolysis
Cholestasis (Biliary obstruction, hepatic infiltration)	ALP *Alkaline phosphatase*	Cholestasis	More indicative of liver disease than GGT	Bone disease, pregnancy
	GGT *Gamma-glutamyl transpeptidase*	Cholestasis, alcohol	More sensitive than ALP May not indicate significant liver disease	Medications, hepatic congestion (CHF)

Monitoring of Liver Chemistry with Medication Use

A thorough medication history is paramount. History should include all prescribed drugs, over-the-counter drugs, as well as natural health products. Almost any medication can cause elevations of liver enzymes and possible liver injury. While the majority of these reactions are idiosyncratic in nature, some are dose-related. Acetaminophen toxicity is dose-related and is the most common cause of medication-induced liver damage and liver failure. For all medications, consult the product monograph for specific information.

- *Monitoring Patients on a Potentially Hepatotoxic Drug*: Certain drugs may require specific monitoring. Please see product monographs.
- *Investigation of Abnormal Liver Tests with Medication Use*: Many hepatotoxic drugs have a "signature" toxicity. In general, any recently started medication or an increased dosage of medication should be considered the primary cause of newly elevated enzymes until proven

otherwise. Consider withdrawing or replacing the drug if the liver chemistry abnormality is severe and it is clinically safe to do so. Repeat test in 1 to 3 months to document normalization.

Isolated Test Abnormality

An isolated minor abnormality (<1.5 times upper limit of normal) in an asymptomatic individual should prompt retesting in 1 to 3 months, particularly after addressing potential causes or modifiable risk factors. GGT elevation is easily induced by alcohol and medications, so an isolated elevation of this enzyme does not always imply significant liver disease.

Isolated indirect (unconjugated) hyperbilirubinemia is commonly due to Gilbert's syndrome, a benign condition that occurs in approximately 2% to 7% of the population, and which is often unrecognised without the provocation of stress or starvation. Less commonly, unconjugated hyperbilirubinemia may be due to hemolysis.

Persistent Minor Elevations of Liver Tests (≥6 months)

Review history for possible exposure to infectious liver disease and other risk factors such as medications or alcohol. If no obvious cause is found, further investigation is indicated (see the table "Common Clues to Diagnose Liver Disease" above). Refer to Viral Hepatitis Testing and Iron Overload – Investigation and Management guidelines and/or consider referral.

Liver Biopsy and Other Special Tests

Disease specific tests including auto-antibodies, copper and iron studies, alpha-feto protein (AFP), and specific viral markers should only be obtained in appropriate circumstances and usually in consultation with a specialist.

A liver biopsy may provide important diagnostic and prognostic information regarding the cause of liver disease. Consultation with a specialist is advisable prior to obtaining a liver biopsy.

In the setting of biliary dilatation, consultation with a specialist is recommended to consider visualization of the biliary tract by computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP).

Serum ammonia levels are seldom useful and should not be obtained.

Evaluation of Hepatic Function

Standard measurements of liver enzymes do not reflect overall liver function. Synthetic function of the liver may be estimated by measuring serum albumin and international normalized ratio (INR).

Bilirubin may be elevated in hepatitis or cholestasis. In chronic liver disease a rising bilirubin may indicate deteriorating liver function.

Acute Presentation with Right Upper Quadrant Pain

In a patient presenting with acute right upper quadrant pain, testing is used to identify potential biliary tract disease. Perform AST, ALT, ALP and GGT testing expeditiously to differentiate between cholestasis and hepatitis. In acute biliary obstruction, levels of ALP and GGT may not be increased for approximately 24 hours.

Urgent referral for an abdominal ultrasound is recommended to identify biliary tract disease.

A patient presenting with fever and right upper quadrant pain may require urgent evaluation for possible biliary tract intervention.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Any condition that results in an abnormal liver chemistry result, including but not limited to:

- Hepatocellular injury (e.g., hepatitis)
- Cholestasis (e.g., biliary obstruction, hepatic infiltration)

Guideline Category

Diagnosis

Evaluation

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Pathology

Intended Users

Clinical Laboratory Personnel

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for the evaluation and interpretation of abnormal liver test results in adults

Target Population

Adults ≥19 years with an abnormal liver enzyme test

Interventions and Practices Considered

1. History and physical examination
2. Risk assessment for liver disease, including medications
3. Assessment of signs and symptoms
4. Laboratory tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT)
5. Differential diagnosis
    - Viral testing (e.g., for hepatitis)
    - Iron overload
6. Management of hepatotoxic medications
7. Frequency of liver enzyme testing
8. Specialist consultation for special testing (e.g., liver biopsy, other laboratory testing, imaging)
9. Liver function tests: serum albumin, international normalized ratio (INR), bilirubin
10. Urgent laboratory testing and ultrasound for acute right upper quadrant pain
11. Urgent evaluation for possible biliary tract intervention for patients presenting with acute right upper quadrant pain and fever

Note: Serum ammonia levels were considered and not recommended.

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Frequency of non-pathological elevated liver enzymes

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Evidence was obtained through a systematic review of peer-reviewed literature (up to June 2011) using the databases MEDLINE, PubMed, EBSCO, Ovid, and the Cochrane Collaboration's Database for Systematic Reviews. Clinical practice guidelines from other jurisdictions for liver chemistry tests, liver enzyme abnormalities, hepatocellular, cholestatic, hepatitis (all types), biliary obstruction, hepatic infiltration were also reviewed (up to June 2011).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This is an evidence based clinical guideline for general practitioners including consensus statements when evidence is not available. It is based on

scientific evidence current as of the Effective Date.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

This is an evidence based clinical guideline for general practitioners with consensus statements when evidence is not available. The type of supporting evidence is not specifically stated for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate evaluation and improved interpretation of diagnostic investigations for abnormal liver chemistry

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

The Clinical Practice Guidelines (the "Guidelines") have been developed by the Guidelines and Protocols Advisory Committee on behalf of the Medical Services Commission (MSC). The Guidelines are intended to give an understanding of a clinical problem and outline one or more preferred approaches to the investigation and management of the problem. The Guidelines are not intended as a substitute for the advice or professional judgment of a health care professional, nor are they intended to be the only approach to the management of clinical problems. The MSC cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please

contact a health care professional.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Medical Services Commission. Abnormal liver chemistry - evaluation and interpretation. Victoria (BC): British Columbia Medical Services Commission; 2011 Aug 1. 5 p. [14 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Aug 1

Guideline Developer(s)

Medical Services Commission, British Columbia - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

Medical Services Commission, British Columbia

Guideline Committee

Guidelines and Protocols Advisory Committee

Composition of Group That Authored the Guideline

Not stated

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Columbia Ministry of Health Web site .

The guideline is also available for mobile devices from the British Columbia Ministry of Health Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 31, 2013. The information was verified by the guideline developer on March 20, 2013.

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